

Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations

Article (Accepted Version)

Rosemann, Achim, Bortz, Gaby, Vasen, Federico and Sleeboom-Faulkner, Margaret (2016) Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations. *Regenerative Medicine*, 11 (7). pp. 647-657. ISSN 1746-0751

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/62396/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations

Authors: Achim Rosemann^{1,2*}, Gabriela Bortz^{3,4}, Federico Vasen^{3,5}, Margaret Sleeboom-Faulkner^{2,6}

Affiliations:

¹Centre for Education Studies, Faculty of Social Sciences, University of Warwick, Coventry CV4 7AL, UK

²Centre for Bionetworking, School of Global Studies, University of Sussex, Brighton, BN1 9SJ, UK

³Institute of Science and Technology Studies, National University of Quilmes (IESCT-UNQ), Roque S. Peña 352, (1876) Bernal, Buenos Aires, Argentina.

⁴National Council of Scientific and Technical Research (CONICET).

⁵Institute of Social Research, National Autonomous University of Mexico, Circuito Mario de la Cueva s/n, Ciudad Universitaria, Coyoacán, 04510 Ciudad de México, México.

⁶Department of Anthropology, University of Sussex, Brighton, UK
Address: Department of Anthropology, University of Sussex, Arts C 206, Brighton, BN1 9SJ, UK

* Correspondence to: A.Rosemann@warwick.ac.uk

Acknowledgments:

This article has benefited from research support provided by the ERC (283219) and the ESRC (ES/I018107/1).

Accepted Version: This is the accepted, post peer-review (but pre publisher layout and copy-editing) version of the paper. Regenerative Medicine accepted the paper on August 12, 2016.

Global regulatory developments for clinical stem cell research: diversification and challenges to collaborations

Abstract

In this article we explore regulatory developments in stem cell medicine in seven jurisdictions: Japan, China, India, Argentina, Brazil, the USA and the European Union. We will show that the research methods, ethical standards and approval procedures for the market use of clinical stem cell interventions are undergoing an important process of global diversification. We will discuss the implications of this process for international harmonization and the conduct of multicountry clinical research collaborations. It will become clear that the increasing heterogeneity of research standards and regulations in the stem cell field presents a significant challenge to international clinical trial partnerships, especially with countries that diverge from the regulatory models that have been developed in the USA and the European Union.

Keywords: Clinical Stem Cell Research, Research Regulation, Evidence-based Medicine, Multi-Country Trials, International Harmonization

Introduction

The regulatory conditions through which stem cell treatments are translated from the lab bench to the clinic and the market are currently in the midst of a renegotiation process [1], [2], [3]. A key problem for the stem cell field is that existing regulatory approaches for the clinical testing and market approval of new drugs do not neatly map onto stem cell interventions. The biological characteristics of stem cells and specific risks for patients require new and tailor-made regulatory frameworks to reliably address scientific and health risks [4]. But the development of regulatory frameworks for stem cell medicine has also been complicated by the widespread availability of unproven or non-systematically tested for-profit interventions with stem cells in many countries [5]. Lucrative business opportunities and widespread demands of patients have resulted in calls for increased access to experimental stem cell interventions and the development of regulatory alternatives. Disagreements have

arisen in particular with regard to the acceptability of experimental stem cell interventions outside of the methodological format of the multiphase randomized controlled trial (RCT), and also the provision of experimental therapies independent from the review of drug regulatory authorities.

The position of the International Society for Stem Cell Research (ISSCR), as published in its recent *Guidelines for Stem Cell Research and Clinical Translation*, is that stem ‘cell based medical products should rarely if ever be developed outside of a formal clinical trials process’ [6]. The ISSCR acknowledges, though, ‘that in some very limited cases, clinicians may be justified in attempting medically innovative stem cell-based interventions in a small number of seriously ill patients’. However, providers of experimental stem cell interventions should ‘under no circumstances’ be allowed to ‘promote, advertise, attempt general recruitment of patients, or commercialize such interventions’ [6].

On the other hand, guidelines from other international societies, such as the International Cellular Medicine Society [7] or the International Association of Neurorestoratology [8] have argued in favour of clinical applications outside of the multiphase clinical trial system [3]. In practice, the provision of commercial clinical stem cell interventions that are offered to patients without systematic clinical research continues to occur on a large scale. McMahon has, in this respect, spoken of the rise of a “global industry” of unproven or non-systematically tested stem cell interventions [5]. She has estimated that in the last fifteen years or so several hundred thousands of patients have received experimental stem cell interventions.

In Part I of this article we will explore how regulatory authorities in the above-mentioned jurisdictions have reacted to these developments. The questions we ask are: what are current developments and trends in the regulation of clinical stem cell interventions and in which ways do these developments challenge the dominant paradigm of evidence-based medicine (EBM) and multi-phase controlled trials in clinical stem cell research. We will show that, even though the clinical evaluation and market approval of stem cell interventions through EBM standards and the use of the multiphase RCT system are still important in many countries, a continuing process of regulatory diversification is underway. Moreover, regulatory arrangements are still evolving in many societies, which has given rise to uncertainties, and which has made efforts of international harmonization more difficult. As we will show, the shift toward regulatory diversification is characterized by three central processes: first, an

increasing number of regulatory exceptions and exemptions, that allows for clinical applications with stem cells outside of the multiphase trial system; second, lenient enforcement of regulatory rules in many countries, which have resulted in the widespread toleration of experimental for-profit practices despite the fact that official regulatory protocols impose the mandatory use of RCTs; third, the emerging of entirely new regulatory models. This is most clearly exemplified by the case of Japan, which in 2014 introduced a model of conditional market approval for stem cell products that allows sidelining the phase I-III clinical trial system.

In Part II we will explore the implications of these processes for international harmonization and the conduct of international clinical research collaborations. We will show that the absence of internationally binding standards for clinical stem cell research presents a huge challenge to multicountry clinical trial partnerships. Four types of challenges will be highlighted and illustrated through a case study of the China Spinal Cord Injury Network (China SCI Net), which has been the first intercontinental clinical trials infrastructure in the stem cell field between the USA and East Asia.

Regulatory comparison

United States of America

The USA was the first country to have issued a formal regulation for clinical use and market approval of stem cell interventions. FDA rules went into effect with the interim rule *Human Cells, Tissues, and Cellular and Tissue-Based Products: Donor Screening and Testing, and Related Labeling*, which was issued on May 25, 2005 [9]. On June 19 2007 this interim rule was adopted as a final rule, without change, and released as the US FDA's *Regulation For Human, Cellular and Tissue Products* (HCT/Ps). [10]. This regulatory framework introduced a risk-based, tiered approach that regulates stem cells as biological products within two categories: "351 products" and "361 products" [10]. The "351" category refers to cells that are more than minimally manipulated and to cells that are used in a non-homologous manner. These cells are classified as a biological drug product and they are subject to US Food and Drug Administration (FDA) pre-market approval. 351 biological products must 'by law [...] go through the multi-phase drug pipeline approval process starting after pre-

clinical studies with an Investigational New Drug (IND) application and proceeding to Phase 1 trials' and then to Phase II and III trials [11].

In a recent effort to create more flexible pathways to market approval of new drugs and biological products, the FDA has introduced since 2012 three types of regulatory exceptions, which can also be granted to human cell and tissue products [11]. These exceptions aim at: (i) speeding up the transition from preclinical to clinical testing ("fast track approval") [12], (ii) accelerated authorization of phase I and II clinical trials that involve seriously ill patients with low life expectancy ("accelerated approval") [13], and (iii) more rapid clinical testing of 'breakthrough therapies' that have the potential to treat a serious or potentially life threatening disease ("breakthrough therapy designation") [14]. In addition to these more recent regulatory exceptions, the FDA offers also a "priority review" procedure, which was introduced in 1992. Priority review aims to expedite the duration of the evaluation process that precedes market approval of a new drug (six instead of ten months), after the completion of the clinical trial period [15]. A fifth regulatory exception is the "expanded access" program (also called "compassionate use program"). This program provides patients access to investigational new treatments parallel to (but outside of) FDA-approved phase II and III clinical trials [16]. The expanded use program dates back to 1987, but was revised in 2009 to ensure 'broad and equitable access to investigational drugs for treatment', including access to biological drug products [17].

The "361" category regulates the use of minimally manipulated stem cells that are applied for homologous use. These cells are not subject to pre-market approval by the FDA and they can be used in patients under compliance with the US human tissue regulation [18]. A large direct-to-consumer market with '361' stem cell products has emerged in the USA in recent years [11]. While many of these clinics purport to offer self-classified '361' products, there have been reports that several of these interventions were actually unproven '351' products which were offered to patients illegally [11]. In response to these claims, the FDA published in November 2015 a draft guidance for a revised and more stringent regulatory approach, which was designed to address this problem [19] [20]. At the time of writing this article, though, this draft guidance was not yet finalized.

Regulatory arrangements for stem cell treatments in the EU are similar to the US model. Cells that are more than minimally manipulated and used in non-homologous contexts are defined as “medicinal products” and are regulated under the *Advanced Therapy Medicinal Products* (ATMP) legislation, which was issued by the European Medicines Agency (EMA) in November 2007. Minimally manipulated autologous stem cells, on the other hand, are regulated under the human tissue legislations of European member states, and not centrally under EMA [21]. The ATMP regulation has harmonized regulatory approaches for clinical stem cell research in EU member states, to enable clinical collaborations and cross-country approval of stem cell products outside of the EU. As in the USA, the EMA regulation demands evidence from systematic clinical studies, typically from multiphase trials. In contrast to the USA, the EU has not experienced the emerging of a large-scale consumer market with minimally manipulated stem cells [22]. However, demands of patients to widen access to stem cell interventions have been addressed through a range of regulatory exceptions and exemptions. As in the USA, the EMA has introduced a “compassionate use” program, which allows access to new drugs and biological products (including stem cell products) outside of premarket clinical trials [23]. Unlike in the USA, however, EMA has also introduced a so-called “hospital exemption” program for stem cell interventions. This program allows the provision of cellular medicinal products to individual patients “in a European hospital under the exclusive professional responsibility of a doctor” [22]. These hospital exemptions are authorized for use by the regulatory authority in the country in which the product is applied. As a result, the hospital exemption scheme has been implemented unevenly across EU member states [1]. In some countries, the scheme has been used to approve large numbers of experimental interventions and has created “the opportunity for a legal market of authorised stem cell therapy products to emerge within the province of the clinical professionalism” [24]. More recently, EMA has also introduced a “conditional market approval” scheme [25], which can be used also for stem cell interventions. According to this scheme, a stem cell product can be licensed at a later stage of a phase III trial, when data collection for efficacy and safety has almost been completed.

Japan

Pre-market evaluation of stem cell therapies in Japan was initially based on a similar regulatory model as in the USA and the EU. Until 2014 stem cell interventions were regulated under the *Pharmaceutical Affairs Law* (PAL) and treated either as pharmaceutical drug products, medical devices or combination products [26]. This regulatory pathway involved systematic multi-phase trials and compliance with good clinical practice (GCP) standards [26]. Then in May 2013 the Japanese National Diet passed the Regenerative Medicine Promotion Act [RMPA] [27], which formed the starting point of a radical regulatory reform. The RMPA was followed by the passing of the Amended Pharmaceutical Affairs Law, which went into effect in November 2014 [28]. Under the amended PAL the conditions for the clinical application of stem cell interventions changed significantly [26]. The amended law allowed for conditional, limited-term market approval of stem cell products after early-phase clinical trials. Conditional approval can occur after positive clinical data from as few as ten patients [29], provided these first-in-human-trials demonstrate that the tested cell products are safe and “likely to predict efficacy” [30]. Once approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA), clinical trial sponsors have the possibility to seek market approval for up to seven years [30]. Clinical efficacy is tested in this time period in post-marketing procedures [31]. This is a significant shift away from the multiphase RCT system, which has emerged as the methodological gold standard in medicine research in the recent decades. This break, and the possibility to time-limited conditional market approval after evidence from small numbers of patients, is likely to have repercussions for the regulation of stem cell research in other countries, and possibly also other fields of medicine research.

It is also noteworthy that conditionally approved stem cell interventions are eligible for reimbursement by the Japanese health insurance system [26]. Costs for these experimental treatments are split between the state and patients at a ratio of 70:30 [30]. This is a drastic change to the financing of research and development (R&D) costs for medicine research, which typically requires long-standing corporate or government investments before development costs could be amortized through health insurance reimbursement and consumer charges.

India

The governance of the clinical stem cell field in India started with the introduction of the *Guidelines for Stem Cell Research and Therapy* [32] a regulatory guidance document that was joint-issued by the Indian Council of Medical Research (ICMR) and Department of Biotechnology (DBT) in 2007 [33]. This regulatory guidance formally prohibited the use of stem cells in human patients, except in the context of formally approved clinical trials [33]. In practice, however, this approach was not consistently implemented and India became one of the countries in which unproven or non-systematically tested stem cell interventions flourished on a large scale [5]. In order to address these problems, the Indian authorities issued a revised regulatory approach in 2013, laid down in the *Guidelines for Stem Cell Research* [34].

These guidelines reconfirmed the prohibition of non-approved commercial applications with stem cells and stated that all clinical trials with stem cells had to be approved by The Drug Controller General India (DCGI). In 2014, the DCGI announced that stem cells were treated as a drug product and that clinical trials and pre-market approval had to conform to the Indian Drugs and Cosmetics Act, which included a new section on stem cells [35]. With these adjustments, the regulation of clinical stem cell research was formally put under statutory law.

At the level of clinic practice, however, the situation remained diverse. Stem cell trials continue to be conducted outside of DCGI control and unapproved or non-systematically proven stem cell interventions are still offered in many hospitals [36]. As a result of this uneven implementation, the current regulatory situation in India can best be described as flexible, and as serving multiple interests and stakeholder groups simultaneously [3]. On the one hand, the DCGI's requirement for multiphase trials and international best practice standards facilitates formal approval and marketization of stem cell-based medicinal products at a national and international level. This is exemplified by the DCGI's approval of the first stem cell product in May 2016, which shall soon also be marketed in the EU, in the context of the EMA's orphan designation scheme [37]. On the other hand, the lack of coherent regulatory enforcement and the continued toleration of unapproved clinical applications [35] enables physician-based forms of innovation and localized forms of profit making outside of the regulatory system.

China

The development of a regulatory framework for clinical stem cell applications in China has been an ongoing process and much slower than for instance in the European Union or the USA. As in India, a large market of experimental for-profit interventions with stem cells emerged in the early 2000s. Following an initial attempt to control the provision of these unproven or non-systematically tested interventions in 2009, which failed [38], the Chinese health authorities introduced a regulatory white paper, in 2013, which formed the basis of a more comprehensive regulatory framework for clinical stem cell research that was publicized in August 2015 [39]. The 2015 *Regulation for Clinical Stem Cell Research*, jointly issued by the National Health and Family Planning Commission (NHFPC) and the Chinese Food and Drug Administration (CFDA), states that the clinical translation of stem cell-based approaches must occur through systematic clinical studies, which must follow from sound pre-clinical evidence. The core of this regulation is that stem cell trials can only be conducted in specifically authorized research hospitals and that for-profit applications of experimental stem cell interventions are legally prohibited. If this rule is implemented, this would mean the delimitation of clinical stem cell interventions to a small number of elite hospitals. It would also mean the systematic shutting down of numerous for-profit stem cell clinics [39]. While this evolving regulatory approach indicates an important step toward the improved review and governance of clinical stem cell research and applications in China, there are still numerous unresolved questions with this framework. A first set of questions concerns implementation: will the Chinese authorities have the political will to mobilize sufficient resources and administrative infrastructures to consistently implement this new regulatory model? Or will informal stem cell interventions continue to exist next to formally approved clinical trials and treatments, as in India and other countries? A second set of questions concerns the exact methodological requirements that will be required in pre-market evaluations. In the 2015 guidelines, this point remained undefined. It is unclear whether stem cells shall be regulated as a pharmaceutical product or a medical technology, and also which types of clinical studies the NHFPC and CFDA require before approving routine clinical use. While the 2013 white paper mentioned phase I–III trials, the 2015 regulation only speaks of clinical studies that shall be conducted according to “scientific principles” [39]. This could well mean that China’s health regulators leave this question deliberately open so as to have the flexibility to follow the current Japanese model rather than the more costly USA or EU model.

Argentina

The clinical use of stem cells is currently regulated under the Ministerial Resolution No. 610/2007 from the Argentinean Ministry of Health. This resolution states that the use of human cells falls under the authority of the Unique Central Institute for Ablation and Implantation (INCUCAI). By falling under the authority of INCUCAI, stem cell interventions are not governed as a medical product (as in the EU, India and the USA) but as a medical procedure, which are managed by the Argentinean Transplant Act. With the exception of haematopoietic cell transplants from human bone marrow, all types of stem cells are considered experimental and require evaluation of safety and efficacy through clinical research [40, 41]. In the late 2000s, a dispute emerged among Argentina's regulators whether stem cells should also be regulated as a medical product. In that case, Argentina's National Administration of Drugs, Food and Medical Technology (ANMAT) would start to play a major role in regulation. A first step into this direction was achieved in 2011 by ANMAT regulation 7075/2011, in which more than minimally modified cellular products were classified as Advanced Therapeutic Medicinal Products (ATMP). At present, however, ANMAT has no legal authority to enforce approval of stem cells treatments under its rule, and it has not been decided in which situation researchers should apply at ANMAT or INCUCAI. Because INCUCAI's regulation does not discriminate between different cell types, specific procedures of cell manipulation, or different levels of risks, the regulation could be considered so broadly as to include even human embryonic stem cells [40]. However, a new regulatory approach that will provide clarity on these issues is currently being drafted by the Ministry of Health (MOH), together with Argentina's Advisory Committee on Stem Cells and Regenerative Medicine [42].

In practice, the legal reach of both INCUCAI and ANMAT is limited. Argentina is a federal country in which national regulatory authorities have legal power only when medical products cross provincial borders or are involved in foreign trade. As a result, federal regulations are not applicable at the provincial level as long as medical treatments or services are applied exclusively within the geographic jurisdiction of a province [40]. A situation exists where there is no effective control over stem cell-based clinical applications if these interventions are not offered or

shipped across multiple provinces. According to estimates of policy experts and representatives of patient associations, this undefined regulatory grey area has resulted in the increase of experimental for-profit interventions with stem cells, which have been provided by at least ten private clinics in the country [43].

Brazil

The development of a regulatory framework for clinical stem cell research in Brazil has been challenging for two reasons: religious opposition to stem cell research, and a constitutional prohibition that bans the commercial use of human cells and tissues [44]. Religious protests first flared up in 2005, when the Brazilian Congress approved Law #11,105, which legitimized the use of human embryonic stem cells (hESC) for research, including in clinical trials. According to this law, the regulation for the production and clinical use of hESC and other types of stem cells (with the exception of bone marrow transplants) fell under the responsibility of Brazil's National Agency for Health Surveillance (ANVISA), the country's national drug regulatory authority [44]. Yet, following a complaint by the Catholic Church at the Brazilian Supreme Court, the authorization of the use of embryos for research purposes was suspended for three years. In 2008, a final verdict confirmed that the 2005 law was valid, and that hESC research could go ahead [45]. According to officials of ANVISA this three-year deliberation delayed the development of effective regulation also for other types of stem cells [44]. A first regulatory step for the clinical use of stem cells was issued by ANVISA in March 2011, in the form of ANVISA Board Resolution #9. However, this regulation specified solely the technical standards for the harvesting, derivation, processing, storage and quality controls for clinical use of stem cells. It did not address standards for clinical trials and market authorization. The reason for this was that the Brazilian constitution prohibits the commercialization of human body materials, including human cells and their derivatives [44]. As a result, market approval and commercial distribution have until to this moment not been permitted. Regulatory debates on this issue within ANVISA and the Brazilian MOH are ongoing. However, because ANVISA has since 2013 worked on a draft regulation for clinical trials for advanced cell products, it is expected that commercialization of stem cell products will ultimately be approved in Brazil [44]. One consequence of this constitutional

prohibition is that the number of for-profit providers of experimental stem cell interventions has been much lower than in other countries [5].

Regulatory diversification: implications for regulatory harmonization

What can currently be observed in the regulatory landscape of stem cell research is a conflict between two central dynamics: the striving for international harmonization, on the one hand, and an increasing process of regulatory diversification, on the other. Attempts of regulatory harmonization are exemplified by the US FDA-EMA-Health Canada Advanced Therapy Medicinal Products (ATMP) Cluster, which since 2008 has focused on the convergence of regulatory protocols for cellular therapies between regulatory authorities in the USA, the EU and Canada [46]. Another example is the Cell Therapy Working Group of the International Pharmaceutical Regulators Forum (IPRF; founded in 2011), which aims to establish best regulatory practices and to realize gradual regulatory harmonization in the cellular medicine field [47]. Like the US FDA-EMA-Health Canada ATMP Cluster, the IPRF Cell Therapy Working Group comprises primarily regulatory authorities from high-income countries, namely the USA, the EU, Canada, Australia, New Zealand, Singapore, Taiwan and South Korea [48].

On the other hand, and in contrast to these ongoing attempts of regulatory harmonization, we are witnessing an increasing dynamics of regulatory diversification. As this paper has shown, this shift toward diversification is exemplified by three central processes. First is the emergence of a growing number of regulatory exceptions and exemptions that were initiated by drug regulatory authorities in high-income countries. These exceptions/exemptions facilitate processes of clinical translation, and sometimes commercial clinical applications [24], outside of the multiphase trial system, but within the confines and review procedures of national regulatory agencies. Salter, Zhou and Datta have described this process as a form of “hegemonic adjustment”, through which national governments have altered regulatory frameworks and clinical methodologies to enable greater responsiveness to health consumer needs [24].

A second process of diversification is flexible enforcement of regulatory rules in some countries, in particular the toleration of clinical for-profit interventions with stem cells outside of the review and control structures of regulatory agencies. This has

happened for years in India and China [49], and in recent years increasingly also in the USA [47], where governments responded only gradually to a flourishing grey-area market of stem cell interventions [49, 50]. Unapproved for-profit applications continue to be tolerated in these countries also after the introduction of national regulatory frameworks, which formally prohibit these experimental interventions. This is the case in both China and India, where large private hospitals and medical corporations continue to offer their services on the Internet and seek to attract “medical tourists” from all over the world [5, 51, 52]. Sleeboom-Faulkner et al. have interpreted this “flexible” or “dual” regulatory approach as an attempt of national governments to serve the interests of domestic and international elite scientists and corporations on the one hand (by introducing regulatory frameworks that comply with EBM and international best-practice standards), and the interests of less well-funded local researchers and companies on the other hand (by tolerating grey-area clinical applications and business practices exterior to formal regulatory rules) [3, 49]. It is of interest that the toleration of unapproved stem cell interventions has not been restricted to middle-income countries, but could also be observed in the USA, where regulators took a surprisingly relaxed approach to many direct-to-consumer [DTC] stem cell clinics [50]. According to Turner and Knoepfler, there are currently more than 350 US businesses offering unapproved DTC interventions with stem cells. These businesses use both allogenic and autologous cells (including xenogeneic and self-proclaimed ‘induced pluripotent stem cells’ and ‘human embryonic stem cells’) for a variety of conditions ranging from ALS, Alzheimer’s and other neurodegenerative diseases, to cardiac diseases, pulmonary disorders, and also cosmetic applications. [50]. This development is partly driven by a growing number of rights-to-try laws in now more than twenty US states, and widespread calls for deregulation from various patient organizations [53]. However, as Turner and Knoepfler suggest, entrepreneurial physicians offering stem cell interventions may also have been emboldened by regulatory inactivity from the side of the FDA [50].

A third process of regulatory diversification in the stem cell field is characterized by the complete abandoning of the multiphase trial EBM system, as has happened in Japan. This model, as Sipp has pointed out, dramatically relaxes the need to demonstrate the clinical utility of cellular products prior to marketing, and raises critical questions regarding the testing of treatment efficacy [30]. According to Sipp, with this new approach ‘Japan clearly hopes to compete and succeed in the race to

build a regenerative medicine industry by flattening a few hurdles' [30]. It is not unlikely that other countries will follow the Japanese regulatory model, or at least create new types of regulatory exceptions in which (conditional) market approval of stem cell treatments can be granted without preceding phase I–III trials. However, as the case of Brazil illustrates, processes of regulatory heterogeneity are not exclusively driven by economic considerations or global competition. In Brazil, divergence from US and EU regulatory models has been caused by religious concerns and a constitutional prohibition to marketize human cell and tissue products. While this situation has not prevented the use of RCT methodology, it has precluded corporate-sponsored trials and participation of Brazilian hospitals and companies in multicountry licensing procedures.

Taken together, the absence of globally shared international regulatory standards for stem cell medicine, and the high level of regulatory diversification that is resulting from differences in national policies as well as ambiguities that stem from emerging or unclear regulatory arrangements, has created crucial challenges for international clinical trial collaborations and cross-country marketing procedures.

Challenges for multicountry stem cell trials

We will now highlight four challenges that result from the above-mentioned situation of regulatory diversification. The first problem is that regulatory variation necessitates ongoing in-depth research into the (changing) regulatory conditions of drug regulatory authorities in several countries. For corporate sponsors and clinical investigators, the diversified and rapidly changing regulatory situation in the stem cell field is often perplexing and gives rise to important organizational problems [54]. What is required is a comparative, long-term engagement with the review and approval criteria of the regulatory agencies in all countries in which a clinical study shall be executed. Differences between regulatory rules in these countries must be singled out at an early stage, so as to design clinical trial protocols that conform to multi-jurisdictional frameworks. This is a time consuming process that is complicated further by language barriers, cultural differences and differences in the ways in which regulatory requirements are enforced [55]. It is complicated further because different types of cells and stem cells are often regulated by different government agencies and different regulatory requirements and rules [56].

A second problem is that the need to interact with multiple regulatory authorities creates a high degree of organizational complexity [54, 57]. To apply for trials and market approval in multiple countries requires time, money, specialist staff, and a substantial administrative infrastructure. This is of course a general problem for clinical trials, not only for stem cell trials. However, because most stem cell trials are sponsored by academic investigators and small-to-mid size biotech companies, who have typically very limited resources, it is often difficult to meet the organizational requirements of multi-country trials, and even more so for researchers and corporations in low or middle-income countries [58].

A third challenge is that evolving or insufficiently defined regulatory procedures can impose significant delays, unexpected costs and uncertainties regarding the planning and conduct of clinical trials [54]. In countries where formal jurisdictional frameworks for cell and stem cell-based clinical interventions are not yet in place or are in an early development phase, the situation can be even more challenging. Drug regulatory authorities may either postpone or completely reject incoming investigational new drug (IND) applications. Emerging or unclear regulatory procedures for the development of stem cell treatments may cause severe problems to international clinical research partnerships. Unresolved regulatory conditions can result in yearlong delays, increase costs, and give rise to the need to relocate a trial to another country or region, necessitating yet more regulatory applications.

A final problem is that regulatory differences between jurisdictions require extensive forms of self-governance, capacity building, training of clinical trial staff and often far-reaching changes of locally evolved conditions and practices in participating trial sites [54, 59]. The reason for this is that regulatory variation between countries has a direct impact on the research practices, clinical methodologies and for-profit strategies that are employed in local hospitals and research institutes. These differences (at the level of local institutions and practices) have to be identified and addressed, so as to warrant standardized implementation of clinical trial protocols and acceptance of clinical data by multiple regulatory agencies. In some countries, knowledge and experience on the conduct of multiphase RCTs is also limited among clinical researchers [60]. These discrepancies between countries, hospitals (and often also within hospitals) endanger the scientific integrity of stem cell-based multi-country trials, and have to be tackled at an early stage of the clinical

translation process [61]. To mitigate this challenge, intensive training of staff and changes in local research practices are required, so that clinical protocols can be implemented in a standardized and trustworthy way [54]. Unless adequate finance for these forms of scientific self-governance, training and education is set aside, the conduct of international multicenter stem cell trials remains a risky undertaking.

Concluding remarks

With a rising number of stem cell-based strategies entering the clinical development phase, the demand for international stem cell trials is growing. This article has shown, however, that the high level of regulatory diversity in the stem cell field provides important obstacles to the organization of multicountry stem cell clinical trials. Emerging and unclear regulations in some countries, and the absence of internationally harmonized regulatory frameworks, confront investigators with unexpected costs, time delays, or even the need to relocate a trial to another country or region. These factors, especially increased or unexpected costs, are likely to reduce possibilities of researchers in low and middle-income countries to participate in the stem cell market, and they are also likely to increase the market price of successfully proven stem cell treatments. The high level of regulatory heterogeneity in the stem cell field gives rise to a high level of administrative complexity, and requires far-reaching forms of scientific self-governance, training, and the creation of effective coordination and monitoring structures. These forms of self-governance and capacity building constitute a fundamental precondition to successfully navigate through a diverse and internationally non-harmonized regulatory environment. It is important to note, in this respect, that the implementation of standardized clinical research protocols is more difficult to achieve in the field of stem cell medicine, than in other – more established – areas of medicine research. The key reason for this – aside from the issue of regulatory heterogeneity – is the lack of well-established international clinical research platforms. In oncology research, for instance, long-standing international clinical research infrastructures have evolved over the course of several decades. These transnational platforms have developed their own centralized institutions that are responsible for the coordination of all successive steps of the clinical translation process, including controls of processes of data collection, recording and analysis [62]. In the stem cell field, however, such infrastructures are

only gradually emerging. While international projects such as the China SCI Net (<http://www.chinascinet.org>) show that multicountry clinical research platforms are evolving, this article has illustrated that these processes are complicated by the absence of internationally harmonized regulatory frameworks. The existence of strongly diverging regulatory, institutional and clinical research cultures across countries and regions makes the performance of standardized multicountry trials a challenging and risky organizational enterprise.

Future Perspectives

The process of regulatory diversification in regenerative medicine research, which has been described in this article, is likely to continue and deepen. With a growing number of regulatory alternatives in the European Union [1] and the USA [11, 50], and the introduction of conditional, limited-term market approval of stem cell products after early-phase trials in Japan [30], the EBM paradigm of medical research (with the multi-phase trial system at its core) seems to gradually lose its hegemonic status [24]. It remains to be seen whether other countries will follow the Japanese regulatory model. However, the emergence of parallel (and potentially incommensurable) regulatory zones and networks [2, 3, 63], in which researchers and companies can choose between different regulatory options to bring stem cell-based treatments to the clinic and market is possible. Of interest is that regulatory heterogeneity in the stem cell field is not only emerging between countries (and in relation to global differentials of wealth, health care as well as scientific and regulatory resources [3]), but increasingly also within national jurisdictions in high-income countries [1, 11, 50, 53]. In the light of the growing pressure from patient organizations, international scientific and economic competition and an increasing market of grey area stem cell interventions [5, 53, 63], the shift toward more rapid, flexible and less rigorous procedures of market approval is likely to continue in many countries, including in the USA and the European Union.

With the increase of regulatory divergence at both national and international levels [2], various questions remain critical. What is the impact of the diversification of regulatory arrangements on the credibility of stem cell therapies, and how do actors determine which standards and products they can trust? Can the scientific and safety standards of medicine research that have evolved during the last few decades (and

which have prevented large numbers of patients worldwide from exposure to fraudulent medicines and intolerable risks) be maintained under the alternative regulatory pathways that are currently emerging? Considering the reputational, financial and health risks of less stringent regulation, the assumption that rapid market approval produces economic advantages, may well prove wrong. Moreover, the adoption of stem cell therapies into national health insurance that lack solid proof of efficacy, is likely to prevent access to other treatments and to take away resources for research and development that may be of greater value in the long run [30]. In the light of these challenges, societies and policy makers are now confronted with the difficult task to find ways and criteria to systematically evaluate methodological alternatives, and to halt them if they are likely to give rise to irresponsible forms of clinical validation, unreliable evidence or (in the most extreme case) the legitimization of for-profit scams. Whether and to what extent policy organs will do so, depends on the political prioritization of this problem, and on the will to mobilize the resources, expertise and administrative infrastructures that are required to perform this task.

References

- [1] Faulkner A. Opening the gateways to market and adoption of regenerative medicine? The UK case in context. *Regenerative Medicine* 11(3), 321-330 (2016).
- [2] Rosemann A, Chaisinthop N. The pluralization of the international: Resistance and alter-standardization in regenerative stem cell medicine, *Social Studies of Science*. doi: 10.1177/0306312715619783 (2015).
- [3] Sleeboom-Faulkner M, Chekar CK, Faulkner A, et al. Comparing national home-keeping and the regulation of translational stem cell applications: An international perspective. *Social Science and Medicine* 153, 240-249 (2016).
- [4] Martell K, Trounson E, Baum E. Stem cell therapies in clinical trials: workshop on best practices and the need for harmonization. *Cell Stem Cell* 7(4), 451-454 (2010).

- [5] McMahon DS. The global industry for unproven stem cell interventions and stem cell tourism. *Tissue Engineering and Regenerative Medicine* 11(1), 1-9, (2014).
- [6] ISSCR. Guidelines for stem cell research and clinical translation (2016).
<http://www.isscr.org/docs/default-source/guidelines/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=2>
- [7] ICMS, Clinical translation of adult stem cell Lines (2010).
http://www.cellmedicinesociety.org/attachments/382_Clinical%20Translation%20of%20Adult%20Stem%20Cells.pdf
- [8] IANR. Standard recommendations for the application of Chinese clinical cell therapy for Neurorestoration. *Cell Transplantation* 22(S1), 5–10 (2013).
- [9] FDA. Human Cells, Tissues, and Cellular and Tissue-Based Products: Donor Screening and Testing, and Related Labeling [70 FR 29939]. May 24, 2005.
<https://www.federalregister.gov/articles/2005/05/25/05-10583/human-cells-tissues-and-cellular-and-tissue-based-products-donor-screening-and-testing-and-related>
- [10] FDA. Regulation For Human, Cellular and Tissue Products (HCT/Ps) [72 FR 33667]. June 19, 2007. <http://www.fda.gov/OHRMS/DOCKETS/98fr/E7-11795.pdf>
- [11] Knoepfler PS. From bench to FDA to bedside: US regulatory trends for new stem cell therapies. *Advanced Drug Delivery Reviews* 82, 192-196 (2015).
- [12] FDA. Fast Track Approval.
<http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm>
- [13] FDA. Accelerated Approval.
<http://www.fda.gov/ForPatients/Approvals/Fast/ucm405447.htm>
- [14] FDA. Breakthrough Therapies.
<http://www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCA/FDASIA/ucm329491.htm>

[15] FDA. Priority Review.

<http://www.fda.gov/ForPatients/Approvals/Fast/ucm405405.htm>

[16] FDA. Expanded Access.

<http://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/default.htm>

[17] FDA. Sub-part 1: Expanded Access to Investigational Drugs for Treatment Use.

<http://www.ecfr.gov/cgi-bin/text-idx?SID=c859616b5a665bbcd13092d0c1c063d&node=sp21.5.312.i&rgn=div6>

[18] Sipp D, Turner L. US regulation of stem cells as medical products. *Science* 338(6112), 1296-1297 (2012).

[19] Draft Guidance for Industry and FDA Staff.

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM469751.pdf>

[20] STAT. FDA moves to crack down on unproven stem cell therapies

<https://www.statnews.com/2016/02/08/fda-crackdown-stem-cell-clinics/>

[21] EMA. Policy on Advanced Therapy Medicinal Products (ATMP) Regulation and the Quality and Safety Regulations (2015).

<https://www.hta.gov.uk/policies/policy-advanced-therapy-medicinal-products-atmp-regulation-and-quality-and-safety>

[22] MacGregor C, Peterson A, Munsie M. Regulation of unproven stem cell therapies – medicinal product or medical procedure? (2015).

<http://www.eurostemcell.org/commentanalysis/regulation-unproven-stem-cell-therapies-medicinal-product-or-medical-procedure>

- [23] EMA. Compassionate Use.
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp
- [24] Salter B, Zhou Y, Datta S. Hegemony in the marketplace of biomedical innovation: Consumer demand and stem cell science. *Social Science & Medicine* 131, 156-163 (2015).
- [25] EMA. Conditional Market Authorization
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000925.jsp&mid=WC0b01ac05809f843b
- [26] Azuma K. Regulatory Landscape of Regenerative Medicine in Japan. *Current Stem Cell Reports* 1(11), 118-28 (2015).
- [27] Government of Japan. The Regenerative Medicine Promotion Act. 2013 Act Nr. 13 (2013) [in Japanese].
- [28] Government of Japan. The Act on the Partial Revision of the Pharmaceutical Affairs Law. 2013 Act Nr. 84 (2013) [in Japanese].
- [29] Cyranoski D. Japan to offer fast-track approval path for stem cell therapies. *Nature medicine* 19(5), 510-510 (2013).
- [30] Sipp D. Conditional approval: Japan lowers the bar for regenerative medicine products. *Cell Stem Cell* 16(4), 353-356 (2015).
- [31] Miyata T. Regulatory and legal frameworks for offering stem cell therapies in Japan (2013).
<https://www.nationalacademies.org/hmd/~/media/Files/Activity%20Files/Research/QualityUnregulatedStemCellTherapies/Miyata%20pdf.pdf>
- [32] Indian Council of Medical Research. Guidelines for Stem Cell Research and Therapy. New Delhi, India: Indian Council of Medical Research (2007).

- [33] Viswanathan S, Rao M, Keating A, Srivastava A. Overcoming challenges to initiating cell therapy clinical trials in rapidly developing countries: India as a model. *Stem Cells Translational Medicine* 2, 607-613 (2013).
- [34] Indian Council of Medical Research. Guidelines for stem cell research. icmr.nic.in/stem_cell_guidelines.pdf (2013)
- [35] Tiwari SS, Raman S. Governing stem cell therapy in India: regulatory vacuum or jurisdictional ambiguity?. *New Genetics and Society* 33(4), 413-433 (2014).
- [36] Bhagavati S. Stem cell therapy: challenges ahead. *The Indian Journal of Pediatrics* 82(3), 286-291 (2015).
- [37] Jayaramam KS. India's first stem cell based drug (2016).
<http://www.natureasia.com/en/nindia/article/10.1038/nindia.2016.61>
- [38] Sui S, Sleeboom-Faulkner M. Governance of Stem Cell Research and Its Clinical Translation in China: An Example of Profit-Oriented Bionetworking. *East Asian Science, Technology and Society*, doi: 10.1215/18752160-3316753 (2015).
- [39] Rosemann A, Sleeboom-Faulkner M. New regulation for clinical stem cell research in China – expected impact and challenges for implementation. *Regenerative Medicine*, Doi:10.2217/rme.15.80. 5-9 (2015).
- [40] Arzuaga FC. Stem Cell Research and Therapies in Argentina: The Legal and Regulatory Approach, *Stem Cells and Development* 22(S1), 40-43 (2013).
- [41] Harmon S, Kale D. Regulating in developing countries: Multiple roles for medical research and products regulation in Argentina and India, *Technology in Society*, 43, 10-22 (2015).
- [42] Ministry of Science, Technology and Innovation of Argentina. Crece el debate sobre las terapias avanzadas en la Argentina. Press Release (2016).
http://www.mincyt.gob.ar/_post/descargar.php?idAdjuntoArchivo=47765

[43] Krmpotic C. Creer en la cura: Eficacia simbólica y control social en las prácticas del Dr. M., *Scripta Ethnologica*, 33, 97-116 (2011).

[44] De Freitas DRC. The Regulatory Pathway for Advanced Cell Therapy and Gene Therapy Products in Brazil, in Galli MC, Serabian M (Eds) *Regulatory Aspects of Gene Therapy and Cell Therapy*, 213-218. Heidelberg and New York: Springer (2015).

[45] Mitre M, Reis B. Science and politics in the regulation of human embryonic stem-cell research in Brazil. *Social Science Information* 54(1), 3-22 (2015).

[46] Arcidiacono JA, Blair JW, Benton KA. US Food and Drug Administration international collaborations for cellular therapy product regulation. *Stem Cell Research Therapy* 3(5), 38 (2012).

[47] IPRF. IPRF Cell Therapy Working Group (2015).
<https://www.i-p-r-f.org/index.php/en/working-groups/cell-therapy-working-group/>

[48] Bedford P, Gillham-Eisen LA. International Regulatory Perspectives: Degree of Regulatory Oversight for Eight Categories of Cell Therapy Products (2015).
https://www.i-p-r-f.org/files/4714/5387/8143/IPRF_Cell_Therapy_WG_Meeting_Report_2013.pdf

[49] Sleeboom-Faulkner M. The large grey area between ‘bona fide’ and ‘rogue’ stem cell interventions—Ethical acceptability and the need to include local variability. *Technological Forecasting and Social Change*. doi:10.1016/j.techfore.2016.04.023, 76-86 (2016).

[50] Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry, *Cell Stem Cell*, doi: 10.1016/j.stem.2016.06.007 (2016).

[51] Song P. Biotech Pilgrims and the Transnational Quest for Stem Cell Cures. *Medical Anthropology*, 29(4), 37–41 (2010).

- [52] Ogbogu U, Rachul C, Caulfield T. Reassessing direct-to-consumer portrayals of unproven stem cell therapies: is it getting better?, *Regenerative Medicine*, 8(3), 361-369 (2013).
- [53] Bianco P, Sipp D. Sell Help not Hope, *Nature* 510(7505), 336-337 (2014).
- [54] Rosemann A. Multi-country stem cell trials: the need for an international support structure. *Stem Cell Research* 14(3), 396-400 (2015).
- [55] Ravinetto RM, Talisuna A, Crop M, et al. Challenges of non-commercial multicentre North-South collaborative clinical trials. *Tropical Medicine and International Health* 18(2), 237-241 (2013).
- [56] Hourd P, Chandra A, Medcalf N, Williams G. Regulatory challenges for the manufacture and scale-out of autologous cell therapies (2014).
<http://www.ncbi.nlm.nih.gov/books/NBK201975/>
- [57] Minisman G, Bhanushali M, Conwit R, et al. Implementing clinical trials on an international platform: Challenges and perspectives. *Journal of the Neurological Sciences* 313(1), 1-6, (2012).
- [58] Keirstead H. Translation of stem cell therapies. Spinal Cord Injury – what are the barriers to cure?. Bedford Center Workshop, Weston Massachusetts, November 9, 2012. <http://www.spinalcordworkshop.org/portfolio-type/hans-keirstead-phd-translation-of-stem-cell-based-therapies/>
- [59] Rosemann A. Standardization as situation-specific achievement: Regulatory diversity and the production of value in intercontinental collaborations in stem cell medicine, *Social Science and Medicine* 122, 72-80 (2014).
- [60] Li MD, Atkins H, Bubela T. The global landscape of stem cell clinical trials. *Regenerative Medicine* 9(1), 27-39 (2014).

[61] OECD. OECD Global Science Forum: Facilitating International Cooperation in Non-Commercial Clinical Trials (2011).

<http://www.oecd.org/science/scienceandtechnologypolicy/49344626.pdf>

[62] Keating P, Cambrosio A. *Cancer on trial: oncology as a new style of practice*. University of Chicago Press (2011).

[63] Sleeboom-Faulkner M. The large grey area between ‘bona fide’ and ‘rogue’ stem cell interventions—Ethical acceptability and the need to include local variability. *Technological Forecasting and Social Change* 109, 76-86 (2016).

Executive Summary

- The regulatory conditions through which stem cell-based medicinal interventions are translated from the lab bench to the clinic and the market are undergoing a significant process of diversification.
- This process has far-reaching consequences for international regulatory harmonization and the organization of multi-country clinical trial collaborations.

Regulatory comparison

- The article explores these issues by examining regulatory developments in seven jurisdictions: Argentina, Brazil, China, the European Union, India, Japan and the USA.

Regulatory diversification: implications for regulatory harmonization

- Regulatory diversification is exemplified by three central processes:
 - A growing number of regulatory exemptions in many countries, which allow for clinical applications outside of the hegemonic multi-phase trial system.
 - Lenient enforcement of regulatory rules in many countries, which have resulted in the widespread toleration of experimental for-profit practices outside of the approval and review mechanisms of drug regulatory authorities.
 - The development of entirely new regulatory models, which have abandoned the use of multi-phase trials as a critical passage point for market approval.
- These developments make processes of multi-country market approval of stem cell-based therapies increasingly difficult.

Challenges for clinical trial collaborations

- The absence of shared regulatory standards for stem cell medicine has created important challenges for international clinical trial collaborations.
- These challenges range from increased costs, time delays, to a high level of administrative complexity and the need for extensive forms of scientific self-governance, staff training and the requirement of effective coordination and monitoring structures (which are necessary to compensate for regulatory gaps between countries).
- These problems are likely to prevent medical progress and make the conduct of standardized multicountry trials to a challenging and risky organizational enterprise.
- They are also likely to delay patients' access to clinically proven stem cell therapies in many countries.